Answer 1:

Bibliographic Information

Clofarabine Acts as Radiosensitizer In Vitro and In Vivo by Interfering With DNA Damage Response. Cariveau, Mickael J.; Stackhouse, Murray; Cui, Xiao-li; Tiwari, Kamal; Waud, William; Secrist, John A., III; Xu, Bo. Department of Biochemistry and Molecular Biology, Southern Research Institute, Birmingham, AL, USA. International Journal of Radiation Oncology, Biology, Physics (2008), 70(1), 213-220. Publisher: Elsevier Inc., CODEN: IOBPD3 ISSN: 0360-3016. Journal written in English. CAN 149:4115 AN 2007:1434423 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Purpose: Combination treatment with radiotherapy and chemotherapy has emerged as the dominant form of cancer adjuvant regimens in recent years. Clofarabine, a newly approved drug for pediatric leukemia, is a second-generation purine nucleoside analog that can block DNA synthesis and inhibit DNA repair. Therefore, we hypothesized that clofarabine could work synergistically with radiotherapy to increase the tumor cell response. Methods and Materials: The effects of clofarabine on radiosensitivity have been established in several tumor cell lines in vitro and in vivo using colony-forming assays and tumor xenografts. The effect of clofarabine on the DNA damage response was also studied in vitro by measuring γ-H2AX focus formation. Results: Clonogenic survival was significantly reduced in irradiated cells treated with clofarabine, demonstrating the strong radiosensitizing effect of clofarabine. Furthermore, clofarabine displayed a radiosensitizing effect that was greater than gemcitabine or 5-fluorouracil. We also found that low doses of clofarabine can prolong the presence of radiation-induced γ-H2AX nuclear focus formation, and high doses of clofarabine can induce DNA double-strand breaks, suggesting that clofarabine can interfere with DNA damage response pathways. In addn., clofarabine-induced radiosensitization was also established in vivo using a colorectal cancer model, DLD-1, in athymic nude mice. When combined with fractionated radiotherapy, a moderate dose of clofarabine led to a significant increase in tumor growth inhibition. Conclusion: Clofarabine acts as a powerful radiosensitizer both in vitro and in vivo by interfering with the DNA damage response.

Answer 2:

Bibliographic Information

Antitumor activity of 2-chloro-9-(2-deoxy-2-fluoro-beta-D-arabinofuranosyl) adenine, a novel deoxyadenosine analog, against human colon tumor xenografts by oral administration. Takahashi T; Kanazawa J; Akinaga S; Tamaoki T; Okabe M Cancer Chemotherapy, Pharmaceutical Research Institute, Kyowa Hakko Kogyo Co. Ltd., Japan Cancer chemotherapy and pharmacology (1999), 43(3), 233-40. Journal code: 7806519. ISSN:0344-5704. Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 9923554 AN 1999120429 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

2-Chloro-9-(2-deoxy-2-fluoro-beta-D-arabinofuranosyl) adenine (Cl-F-araA) is a novel deoxyadenosine analog, which inhibits DNA synthesis by inhibiting DNA polymerase alpha and ribonucleotide reductase. Cl-F-araA shows potent antiproliferative activity against several leukemic cell lines including those of human origin and is also effective against murine solid tumors, in particular being curative against colon tumors. PURPOSE: We therefore decided to investigate whether Cl-F-araA is effective against human colon tumors, in particular by oral administration, since it has improved stability compared with other deoxyadenosine analogs. METHODS: Antiproliferative activity in vitro was determined from cell counts. Subcutaneously inoculated xenograft models and a liver micrometastases model were used for assessment of antitumor activity in vivo. RESULTS: Cl-F-araA showed potent antiproliferative activity against four human colon tumor cell lines (HCT116, HT-29, DLD-1, WiDr), with a 50% growth-inhibitory concentration (IC50) of 0.26 microM with a 72-h exposure. This activity was greater than those of fludarabine desphosphate and cladribine, other deoxyadenosine analogs, which showed IC50 values of 19 microM and 0.35 microM, respectively. Cl-F-araA showed potent antitumor activity against four human colon tumor xenograft models (HT-29, WiDr, Co-3, COLO-320DM) in a 5-day daily administration schedule, which was shown to be the most effective of three administration regimens tested (single, twice-weekly, 5-day daily). In particular, oral administration showed significantly superior activity, with a regressive or

cytostatic growth curve, compared with intravenous administration. In addition, Cl-F-araA was effective at only one-sixteenth of the maximum dose tested in a 10-day daily administration schedule. Therapeutic efficiency seemed to increase in proportion to the frequency of administration.
Cl-F-araA also decreased liver micrometastases created by intrasplenic injection of human colon tumor cells, leading to complete suppression at the maximum dose tested. CONCLUSIONS: These results suggest that Cl-F-araA might be clinically effective against human colon cancers using a daily oral administration schedule.